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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/873,555	06/04/2001	Michael Joseph Luzzio	PC10795A	7601

7590 04/25/2005

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EXAMINER	
RAO, DEEPAK R	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 04/25/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/873,555	LUZZIO ET AL.	
	Examiner	Art Unit	
	Deepak Rao	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 October 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6-10,12-14,29,34-39,44-49 and 59-68* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1,6-10,12-14,29,34-39 and 44-48* is/are allowed.

6)☒ Claim(s) *49, 59-68* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to the amendment filed on October 7, 2004.

Claims 1, 6-10, 12-14, 29, 34-39, 44-49 and 59-68 are pending in this application.

Withdrawn Rejections/Objections:

Applicant is notified that any outstanding rejection/objection that is not expressly maintained in this office action has been withdrawn or rendered moot in view of applicant's amendments and/or remarks.

The following rejections are maintained:

Claims 49 and 59-68 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating carcinoma, does not reasonably provide enablement for a method of treating hyperproliferative disorder generally; or a method of preventing blastocyte implantation; or a method for treating a disease related to vasculogenesis or angiogenesis. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The reasons provided in the previous office action are incorporated here by reference. (Claim 49 is included here because the claim recites 'composition for the treatment of hyperproliferative disorder').

Applicant's arguments have been fully considered but they were not deemed to be persuasive. Applicant argues that 'the specification sets forth in detail on pages 1-2 and 25-26 that the compounds of the invention inhibit tyrosine kinase and such activity is correlated with

the treatment of the various disorders of the claims'. First, applicant has not provided any convincing evidence to support the instantly claimed method of treating all types of hyperproliferative disorders, including all types of cancer. Applicant argues that 'inhibition of tyrosine kinases will be useful in the treatment of abnormal cell growth and in particular cancer', however, tyrosine kinases represent various members of the protein kinase super family. There is neither data on how many compounds were tested nor data on which enzymes were inhibited and which ones were not. Applicant did not state on record or provide any guidance that the assays provided are correlated to the clinical efficacy of the treatment of various disorders of the claims. As can be seen from specification page 26, the *in vitro* data holds significant role in determining the dosage regimen based on the minimal effective concentration of each of the compound to achieve the desired inhibition of the protein kinases.

Contrary to what applicant urge by citing *In re Marzocchi*,169 USPQ 367, the examiner has provided both reasoning including the nature of the invention, which is directed to an unpredictable art as well as relevant publication to support the reason for the rejection. Applicant(s) has not specifically addressed the issue. As stated in the previous action, specification provides no evidence to show enablement for treating cancer generally. Where the utility is unusual or difficult to treat or speculative, the examiner has authority to require evidence that tests relied on are reasonably predictive of *in vivo* efficacy by those skilled in the art. See for example *In re Ruskin* 148 USPQ 221; *Ex parte Jovanovics* 211 USPQ 907. Applicant has not provided any reference(s) that forms sufficient evidence that claimed uses were art-recognized based on activity relied on at the time of applicants' effective filing date. MPEP 2164.05(a).

For the instant situation, *In re Buting*, 163 USPQ 689 (CCPA 1969), is on point and more applicable to the instant claims wherein 'evidence involving a single compound and two types of cancer, was held insufficient to establish the utility of the claims directed to disparate types of cancers. The judges in that case indicated that "We are not aware of any reputable authority which would accept appellant's two clinical cases as establishing utility for treatment of cancer in humans. As was pointed out in *Brenner v. Manson*, 148 USPQ 689, a process to be patentable must produce a useful result and be of substantial utility not merely of scientific interest or for further testing. In this case further testing seems necessary".

Further, claim 66 recites "a method of prevening blastocyte implantation" which is not adequately enabled solely based on the activity related to tyrosine kinase inhibition. Applicants provide no competent evidence for the scope of the above claim. "To prevent" actually means *to anticipate* or *counter in advance, to keep from happening etc.* (as per Websters II Dictionary) and therefore it is not understood how one skilled in the art can reasonably establish the basis and the type of subject to which the instant compounds can be administered in order to have the "prevention" effect. The specification provides test assays to measure the in vitro activity of the compounds in inhibiting KDR/VEGF, however, it is inconceivable from this data as to how the claimed compounds can not only treat various disorders but also "prevent" the instantly recited blastocyte implantation. Further, there is no evidence on record which demonstrates that the *in-vitro* screening tests relied upon are recognized in the art as being reasonably predictive of success in any of the contemplated areas of "prevention". Such a reasonable correlation is necessary to demonstrate such utilities. See *Ex parte Stevens*, 16 USPQ 2d 1379 (BPAI 1990); *Ex parte Busse et al.*, 1 USPQ 2d 1908 (BPAI 1986) (the evidence must be accepted as

"showing" such utility, and not "warranting further study"). The evidence presented in this case does not show such utilities related to "prevention", but only warrants further study.

Next, applicant's attention is drawn to the Revised Interim Utility and Written Description Guidelines, at 64 FR 71427 and 71440 (December 21, 1999) wherein it is emphasized that 'a claimed invention must have a specific and substantial utility'. The disclosure in the instant case is not sufficient to enable the instantly claimed 'preventive' effect solely based on the inhibitory activity disclosed for the compounds.

Further, the instant claim 67 is drawn to 'a method for treating a disease related to vasculogenesis or angiogenesis'. "Angiogenesis" is the process of vascularization of a tissue involving the development of new capillary blood vessels and therefore, is not seen as being a disease or disorder, but as an absolutely essential body process. Angiogenesis is a multi-faceted process involving heterotypic interactions between various cell types. Angiogenesis is the driving force behind tumor growth and metastasis. Regarding therapeutic perspectives with respect to angiogenesis, Carmeliet et al. (Nature 2000) provide that "Whether this abnormal vascular morphology can lead to impaired microcirculation is not known. Furthermore, it is not known whether increased systemic levels of angiogenic cytokines during the course of these therapies will alter the expression of adhesion molecules in systemic circulation, trigger dormant tumors, and/or accelerate atherosclerosis".

While the specification provides sufficient enabling disclosure for the synthesis of the instantly claimed compounds, does not provide an enabling disclosure sufficient to cover the entire scope of the methods of use recited in the instant claims. The instant claims include 'treatment of several types of diseases having diverse mechanisms - affecting different organs

and having different methods of growth or harm to the body, and different vulnerabilities'. For example, the development of the most efficacious strategy for the treatment of cancers is based on understanding the underlying mechanisms of carcinogenesis. This includes the knowledge that the carcinogenic process is a multi-step, multi-mechanism process and that no two cancers are alike, in spite of some apparent universal characteristics, such as their inability to have growth control, to terminally differentiate, to apoptose abnormally and to have an apparent extended or immortalized life span. Since tumor promotion phase involves multiple mechanisms, there is no existence of a single therapeutic approach.

Applicant relies on Kelloff reference as a state of the art reference to support the instant claims. However, the reference does not identify a single class of compounds that can treat all types of diseases of the instant claims. Further, one skilled in the art of medicinal therapy recognizes that there are complex interactions between individual genetic, developmental state, sex, dietary, environmental, drug, and lifestyle factors that contribute to the carcinogenic process, making it even more challenging to have a single therapeutic agent for the treatment of diverse diseases. As can be seen from applicant's cited Kelloff reference, 'a possible testing strategy for the development of EGFR inhibitors as chemopreventive agents includes several steps – (a) determine the EGFR inhibitory activity *in vitro*; (b) evaluate EGFR specificity and selectivity; (c) determine EGFR-mediated effects in intact cells; (d) determine EGFR-mediated effects *in vivo*; and (e) determine chemopreventive efficacy *in vivo*', see the abstract. Rigorously planned and executed clinical trials, incorporating measurement of appropriate biomarkers and pharmacodynamic endpoints are critical for selecting the optimal dose and schedule. A detailed understanding of the molecular mode of action of the kinase inhibitors alongside the elucidation

of the molecular pathology of individual cancers is required to identify tumor types and individual patients that may benefit most from treatment. It is also important to construct a pharmacologic audit trail linking molecular biomarkers and pharmacokinetic and pharmacodynamic parameters to receptor response endpoints. Therefore, it is maintained that applicants have not provided sufficient test assays or data to support treatment commensurate in scope with the claims, as of the filing date of the application.

Allowable Subject Matter

Claims 1, 6-10, 12-14, 29, 34-39 and 44-48 are allowed. The references of record do not teach or fairly suggest the instantly claimed compounds.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

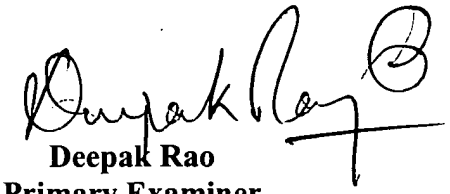
A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deepak Rao whose telephone number is (571) 272-0672. The examiner can normally be reached on Tuesday-Friday from 6:30am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Mukund Shah, can be reached on (571) 262-0674. If you are unable to reach Dr. Shah within a 24 hour period, please contact James O. Wilson, Acting-SPE of 1624 at (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Deepak Rao
Primary Examiner
Art Unit 1624

April 18, 2005